REMARKS

Reconsideration and allowance are respectfully requested.

Claims 15-19, 24-31 and 35-40 are pending. The amendments are supported by the original disclosure and, thus, no new matter is added by their entry. Support for the amendment to claim 27 may be found at page 10, lines 16-23, and page 11, lines 1-5, of the specification. See also the former claim 34, the limitations of which are incorporated in the present claim 27. The format of the Markush group is corrected.

Applicants submitted an Information Disclosure Statement (IDS) on February 17, 2006. Copies of all non-U.S. patent documents were submitted. They were received by the PTO as confirmed by the undersigned's inspection of the Image File Wrapper. To facilitate entry into the record, they will be relisted on a Form PTO-1449. In response to the Examiner's requirement, the titles of non-patent documents will also be listed on the Form PTO-1449.

Restriction Requirement

It was alleged on page 2 of the Office Action, "The specification does not limit the definition of derivatized and functionalized polymer. Broadest reasonable interpretation of this claim term encompasses $NH_2CH_2CH_2Ph$ group which is a derivatized from of polyethylene glycol." Applicants disagree with these allegations. In particular, the skilled artisan would not recognize $NH_2CH_2CH_2Ph$ group as a derivatized and functionalized polymer. What chemical reaction(s) would derive $NH_2CH_2CH_2Ph$ from PEG? More importantly, claim 27 refers to "homo- or co-polymers optionally being derivatized or functionalized" (emphasis added). Therefore, either X or X' is required to be a homo- or co-polymer. $NH_2CH_2CH_2Ph$ is not a polymer. Thus, $NH_2CH_2CH_2Ph$ cannot be X or X'.

35 U.S.C. 101/112 –Utility

Only after the Patent Office provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. *In re Brana*, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995). Even if a person

of skill in the art would have reasonably questioned the asserted utility, declaration evidence alone, which shows that compounds within the scope of the invention exhibited the asserted utility, is sufficient to satisfy the burden shifted to the applicant. *Id.* at 1441-42.

Claim 35 was rejected under Sections 101 and 112 because it is allegedly not supported by either a specific or substantial asserted utility or a well established utility. It was further alleged that one skilled in the art would not know how to use the invention. Applicants traverse.

Within the scope of claim 35 are therapeutic proteins conjugated to polyethylene glycol. Protein-based medicines are well known in the pharmaceutical arts. But native proteins may be immunogenic, proteolyzed after administration, and eliminated from the body. Thus, a patient's tolerance of the pharmaceutical, as well as its bioavailability and pharmacokinetics, may be improved by conjugation of protein with a polymer like PEG. See pages 1-2 of Applicants' specification. For the specific case of PEG, this process is known as pegylation and the conjugated protein is referred to as pegylated.

It was also known that many of the prior art's polymer reagents and processes for their conjugation to proteins suffer from drawbacks: e.g., hydrolytically unstable polymeric conjugating reagents and impairment of the protein's biological function. See pages 2-3 of Applicants' specification. Applicants have discovered a novel process that provides stoichiometric and site-specific conjugation of protein with polymer using thiol linkages. "This technology provides clear advantages over known techniques for conjugating polymers to proteins" (page 6 of Applicants' specification).

Disulfide bonds are found in therapeutic proteins such as, for example, secretory proteins, lysosomal proteins, and the exoplasmic domains of membrane proteins. Applicants teach specific proteins on pages 18-20 of their specification. Further, at the top of page 18 of Applicants' specification, they disclose the practical utility of using the conjugated protein in a pharmaceutical composition. This utility is well established for therapeutic proteins. In Example 7, interferon alpha 2a was conjugated and its activity after conjugation was demonstrated. Its therapeutic use is well known to the skilled person.

Finally, no evidence was presented in the Office Action that the skilled person would not have found this utility credible.

Withdrawal of the Section 101/112 rejections is requested because Applicants have taught that the claimed invention has a credible, specific, and substantial utility. Their disclosure would also teach a skilled person, who possesses general knowledge available in the art, how to use the claimed invention.

35 U.S.C. 112 – Written Description

The specification must convey with reasonable clarity to persons skilled in the art that applicant was in possession of the claimed invention as of the filing date sought. See *Vas-Cath v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). But the Patent Office has the initial burden of presenting evidence or a reason why persons of ordinary skill in the art would not have recognized such a description of the claimed invention in the original disclosure. See *In re Gosteli*, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989).

Claims 15-36 (this appears to be a typographical error because claims 15-26 and 36 were withdrawn by the Examiner) were rejected under Section 112, first paragraph, as allegedly failing to comply with the written description requirement. It was further alleged, "The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Applicants traverse because the specification teaches a representative number of species within the claimed genus.

The objection to "derivatized or functionalized" to describe X and X' is mooted by deletion of the phrase. Since this phrase is an optional limitation, the scope of claim 27 is not altered by deletion. The term "polymer" includes those forms that are derivatized or functionalized, but the claimed invention is no longer limited to them because the genus of polymers is claimed broadly. The genera of polymers X and X' includes the specific homo- or copolymers listed in the Markush group. The latter are representative species within the claimed genera. But the skilled person would understand that other

polymers are also included within the claimed genera, including those that are derivatized or functionalized.

The Examiner also objected to "moiety preparable by reduction of an electron-withdrawing group" to describe W. Her attention is directed to page 15, line 16, to page 16, line 4, of Applicants' specification where they teach that the immediate product of the reaction is a conjugate which contains an electron-withdrawing group (because the electron-withdrawing group is needed for the reaction to proceed). Such compounds, however, may be susceptible to decomposition because the process is reversible under some conditions. Reducing the electron withdrawing group removes the possibility of this reverse reaction and produces a stable conjugate, which is desirable for reasons discussed above. Several specific examples of electron withdrawing groups and their reduction products are given in Applicants' specification. On page 6 of the Office Action, there was an objection that the specification does not describe embodiments wherein X' is a polymer and X-Q-W is an electron-withdrawing group. When X' is a polymer and X-Q-W is an electron-withdrawing group (e.g., a cyano group), they are chemically equivalent to the situation in which X is a polymer and W is an electron-withdrawing group. A specification need not teach, and preferably omits, what is well known in the art. See *Hybritech v. Monoclonal Antibodies*, 231 USPQ 81, 94 (Fed. Cir. 1986). Applicants submit that the skilled person would not need to be taught well-known chemical principles.

The objection to "group derived from a biological molecule" to describe Z^1 and Z^2 is mooted by deletion of the phrase. Z may be any single protein.

Withdrawal of the written description rejection made under Section 112, first paragraph, is requested because the specification conveys to a person skilled in the art that Applicants were in possession of the claimed invention as of the filing date.

35 U.S.C. 112 – Definiteness

Claims 27-35 were rejected under Section 112, second paragraph, as allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention." Applicants traverse because of the amendment of claim 27 and the above explanations rebutting the written description rejection

The objection to "derivatized or functionalized" to describe X and X' is mooted by deletion of this optional limitation. It is not required for patentability.

As explained above, "moiety preparable by reduction of an electron-withdrawing group" to describe W is not vague or indefinite. Applicants' specification at page 15, line 16, to page 16, line 4, teaches that the immediate product of the reaction is a conjugate which contains an electron withdrawing group (because the electron withdrawing group is needed for the reaction to proceed). Such compounds, however, may be susceptible to decomposition because the process is reversible under some conditions. Reducing the electron withdrawing group removes the possibility of this reverse reaction. Thus, a stable conjugate is produced. Finally, claim 27 is directed to a product. Thus, reciting additional steps in a preparation method does not place limits on the claim as alleged on page 7 of the Office Action.

The objection to "group derived from a biological molecule" to describe Z^1 and Z^2 is mooted by deletion of this limitation. It is not required for patentability. Z may be any single protein.

Applicants request withdrawal of the Section 112, second paragraph, rejection because the pending claims are clear and definite.

35 U.S.C. 102 – Novelty

A claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is claimed. See *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Claim 27 was rejected under Section 102(b) as allegedly anticipated by Wilbur et al. (Bioconjugate Chem. 5:220-235, 1994). Applicants traverse.

Wilbur fails to teach or suggest a conjugate comprising a polymer as required by the claimed invention. As explained above, the skilled person would have no reason to

believe that the $NH_2CH_2CH_2Ph$ group is derivatized polyethylene glycol because that group is **not** a polymer. Since the independent claim is established to be novel, all of the dependent claims are also novel over Wilbur.

Further, Wilbur describes a process in which *two separate* antibody fragments are each covalently bonded to a trifunctional agent by a *single* sulfur atom derived from cysteine from each antibody fragment. Hence, each antibody fragment is covalently bound *at one point only* to the trifunctional agent. Such an arrangement would teach away from Applicant's claimed invention in which Z is a *single* group.

Claim 27 was rejected under Section 102(b) as allegedly anticipated by Kornfield et al. (J. Org. Chem. 19:1671-1680, 1954). Applicants traverse.

Kornfield fails to teach or suggest a conjugate comprising a polymer as required by the claimed invention. Nor does Kornfield disclose a conjugate comprising a protein. Although these distinctions are sufficient to demonstrate the patentability of the pending claims, Applicants record their disagreement with the interpretation of the claims used in the Office Action.

Withdrawal of the Section 102 rejections is requested because the cited documents fails to disclose all limitations of the claimed invention.

Conclusion

As further evidence of the patentability of the pending claims, Applicants submit portions of two textbooks as evidence of what one of ordinary skill in the art knew when Applicants made their invention and two Rule 132 Declarations. Prof. George provides an expert's opinion on the surprising results achieved by the claimed invention. Prof. Antony Godwin provides additional evidence of the general applicability of the claimed invention to a variety of proteins.

Analytical Chemistry for Technicians sets out succinctly at page 472, "The four R group interactions are: 1) hydrophobic interactions, 2) ionic (charge) attractions, 3) hydrogen bonding, and 4) disulfide bonds between cysteine residues (amino acids in a chain). Since disulfide bonds are the only covalent linkages, their presence is deemed

crucial for protein stability." In other words, the skilled person believed that a protein's stability would be destroyed by breaking a disulfide bond therein.

Similarly, the section entitled "The Role of Disulfide Bridges" in *Organic Sulfur Chemistry: Biochemical Aspects* at page 147 states, "When all the disulfide bridges in a protein are reduced, both the structure and function are generally lost completely."

Prof. Andrew George (who is an extremely experienced and distinguished expert in this field) makes the same point in his declaration. He recounts how, when he was first told of the present invention by one of the inventors, Prof. Shaunak, he did not believe that the invention would work. He was surprised by the successful results obtained when PEGylating interferon, and asked to see a copy of the paper which Prof. Shaunak and others were planning to submit to Nature. Prof. George has attached a copy of this paper, which was published in 2006 in Nature Online, and also an article published in Hospital Doctor at around the same time, to his Declaration. Both papers make the point that it is very surprising that activity can be maintained despite the fact that a disulfide bridge is broken in the protein.

Therefore, Applicants submit that one of ordinary skill in the art would not have attempted to improve a process for conjugating a protein to a polymer by designing an intermediate for use in a process which involves the breaking of a disulfide bridge to link a *single* protein to a conjugating reagent. The resulting conjugates are novel, and establish a level of biological activity which would be very surprising to one of ordinary skill in the art. By contrast, the prior art of record shows that a reasonable expectation of success was lacking when Applicants made their invention and taught away from that invention.

As well as those proteins already disclosed in Applicants' specification (i.e., ribonuclease A, IgG Fab fragment, asparaginase, and interferon,), many additional protein conjugates have been made to prove the generality of the process for preparing them. Attached is a declaration from Dr. Antony Godwin, which confirms this by using the same reactions. Dr. Godwin confirms that the Applicants have successfully prepared pegylated conjugates of all of the following additional proteins: interferon alpha 2a (cytokine), erythropoetin (cytokine), anti-CD4 Fab (antibody fragment), anti TNFα single

domaine Fab (antibody fragment), leptin (hormone), lipase (enzyme), integrin binding peptide, and blood factor protein. In all these cases, the pegylation was successful, and in all these cases, biological activity was retained following pegylation.

Therefore, one of ordinary skill in the art would not have believed that Applicants' process would have been successful at the time their invention was made. He would have believed that breaking a disulfide bond in a protein, in order to conjugate a single protein to a conjugation reagent, would destroy the protein's activity.

For these reasons, the pending claims are clearly patentable over the prior art of record. Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if additional information is required.

Respectfully submitted,

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